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# Idiopathic Thromobocytopenic Purpura in Two Mothers of Children With DiGeorge Sequence: A New Component Manifestation of Deletion 22q11?

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**The phenotypic spectrum caused by the microdeletion of chromosome 22q11 region is known to be variable. Nearly all patients with DiGeorge sequence (DGS) and approximately 60% of patients with velocardiofacial syndrome exhibit the deletion. Recent papers have reported various congenital defects in patients with 22q11 deletions. Conversely, some patients have minimal clinical expression. Ten to 25% of parents of patients with DGS exhibit the deletion and are nearly asymptomatic. Two female patients carrying a 22q11 microdeletion and presenting with idiopathic thrombocytopenic purpura are reported. Both had children with typical manifestations of DGS. Am. J. Med. Genet. 69:356–359, 1997.** © 1997 Wiley-Liss, Inc.

**KEY WORDS: DiGeorge sequence; deletion 22q11; idiopathic thrombocytopenic purpura; immune dysfunction**

## INTRODUCTION

The phenotypic expression of the microdeletion of chromosome 22 within the 22q11 region is known to be highly variable [Driscoll et al., 1993; Wilson et al., 1993; Levy-Mozziconnacci et al., 1994]. Most patients reported to date have the DiGeorge sequence (DGS) or velocardiofacial syndrome (VCFS). These two conditions have been described separately and are clinically different but with some degree of overlap. Patients with milder clinical pictures, either isolated congenital conotruncal cardiac defects [Goldmuntz et al., 1993; D'Angelo et al., 1994] or hypoparathyroidism [Sciré et al., 1994] have been reported. In 10 to 25% of cases, one of the parents is found to be a carrier of the deletion [Wilson et al., 1993]. Most of these parents are nearly asymptomatic. We report on two families in which the mothers exhibit the deletion and have idiopathic thrombocytopenic purpura (ITP).

## CLINICAL REPORTS

### Family 1

The mother was born in 1967. She had learning disability and speech difficulties, with hypernasal voice. Physical examination showed large nose, short and poorly defined philtrum, and small ears with an overfolded helix (Figs. 1 and 2).

At age 20, she developed severe thrombocytopenia with less than 10,000 platelets per $mm^3$. ITP was diagnosed on the following criteria: spleen and liver were not enlarged, the megakaryocyte number was increased in bone marrow smears with apparently normal granulopoiesis and erythropoiesis, HIV serology was negative, the sedimentation rate was normal, and there were no antinuclear antibodies. Isotopic study of platelet survival with $^{51}Cr$ radiolabelled alloplatelets showed a markedly decreased lifespan (less than 1 day) and an almost exclusive splenic sequestration. Interestingly, this woman also had chronic leuconeutropenia with WBC counts ranging from 1,900 to 4,000/$mm^3$ on different examinations, and neutrophil counts between 500 and 2300/$mm^3$ and lymphocyte counts between 900 and 2,300/$mm^3$ (Table I). The patient received several courses of corticotherapy and intravenous immunoglobulin, which only resulted in transient improvements of the thrombocytopenia. Finally, she underwent splenectomy and had complete recovery of her platelet counts. Two years after splenectomy, the last blood count showed 187,000 platelets. The mean platelet volume was slightly increased (11.5 $\mu m^3$) but there were no giant platelets. A flow cytometry study of platelet glycoproteins, using monoclonal antibodies specific for GPIb, GPIIb/GPIIIa, and GPIa/IIa, showed a normal expression of these glycoproteins. The lymphocyte count was 2,480/$mm^3$ with 1,580 CD3+ cells/$mm^3$.

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Fig. 1, 2. Frontal and profile view of the mother of family 1, showing bulbous nose, short philtrum, and small ears.

In 1993, she became pregnant. Pregnancy and delivery were uneventful. At birth, the child had heart murmur. Interrupted aortic arch and VSD were diagnosed. The boy had minor facial anomalies, with round face, upslanted palpebral fissures, hypertelorism, small mouth, and small and malformed ears (Fig. 3). Transient hypocalcemia was documented. The congenital heart defect was repaired at age 1 month. DGS was suspected.

Fluorescent in situ hybridization (FISH) with cosmid probes sc4.1 and sc11.1, specific of the 22q11 region, was performed according to the methods previously described [Levy-Mozziconnacci et al., 1994]. Cosmid probes were labelled by nick-translation with biotin 11-dUTP, according to BRL protocol. The hybridization signal was evoked by FITC labelled-avidin, amplified twice with additional layers of biotinylated goat anti-avidin and avidin-FITC, and chromosomal DNA was counterstained by propidium iodide. The mother and child were deleted for both loci.

### Family 2

In this family, the first child, born in 1991, had DGS with interrupted aortic arch, VSD, hypocalcemia, and absent thymus. No molecular studies were conducted. This child died at age 1 month and the couple was referred for genetic counseling. The 25-year-old mother was found to have a long nose and a nasal speech (Fig. 4). Personal history documented developmental delay. She walked at age 4 years.

A low platelet count was detected at age 26 years, during her second pregnancy. Thrombocytopenia was moderate (platelet counts between 90,000 and 120,000/mm$^3$) but chronic, now persisting for 3 years after the initial evaluation. There was no hepatosplenomegaly and antinuclear antibodies were negative. Considering these facts, the woman was thought to have mild ITP which did not require any treatment.

The child, a girl, was born by C-section. She exhibited severe neonatal hypocalcemia with seizures. There was no visible thymic shadow on X-ray films. Facial appearance was typical of DGS. Transient thrombocytopenia was observed during the first days of life, as is usual in neonates born to mothers with ITP. This thrombocytopenia was successfully treated with intravenous immunoglobulins. FISH analysis of the 22q11 region demonstrated deletion in both mother and child.

## DISCUSSION

The clinical spectrum of microdeletion 22q11 has widened. It is now recognized that such a deletion can lead to a variety of phenotypes. DGS, characterized by thymic hypoplasia, hypocalcemia, congenital heart defect of conotruncal type, and typical facies, represents the more severe phenotype [Wilson et al., 1993]. VCFS,

TABLE I. Hematological Findings

| | Mother of family 1 | | | |
|---|---|---|---|---|
| | Before splenectomy | | After splenectomy | Mother of family 2 |
| Platelet count[a] | 8,000 | 11,000 | 187,000 | 120,000 |
| WBC count[a] | 2,400 | 1,900 | 3,400 | 6,000 |
| Neutrophil count[a] | U* | 800 | 310 | 4,740 |
| Lymphocyte count[a] | U | 900 | 2,480 | 1,020 |
| Monocyte count[a] | U | 150 | 540 | 250 |
| CD3+ lymphocytes[a] | U | U | 1,580 | U |

* U, unknown.
[a] Per mm$^3$.

Fig. 3. Frontal view of the child of family 1. Note the small mouth.

described in 1978 by Shprintzen et al. in patients with velopharyngeal insufficiency, congenital heart defect, and learning disabilities is also found to be associated with 22q11 deletion in most cases. Wilson et al. [1993] proposed the acronym CATCH 22 (Cardiac defects, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia) to describe the clinical spectrum of microdeletion 22q11. However, these five letters are far from describing all the component manifestations that can be found in patients hemizygous for 22q11. A variety of other congenital defects have been reported in patients with DGS [Wilson et al., 1993; Nickel et al., 1994]. Studies of patients with VCFS have shown that late-onset disorders, such as psychosis, can complicate the prognosis of these children. Conversely, very mild forms have been reported [Lipson et al., 1994], including 10 to 25% of parents of children with DGS, who exhibit the molecular defect and represent the milder end of the phenotype.

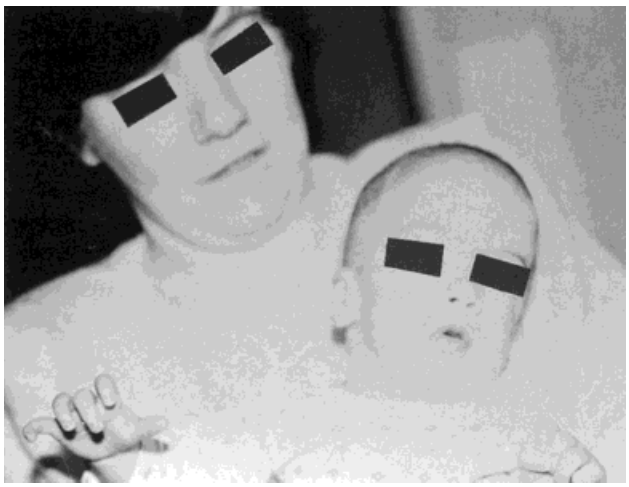

Fig. 4. Frontal view of family 2, mother and child. In the mother, the nose is typical with a large and prominent root.

We present two cases of mothers whose 22q11 hemizygosity was detected after the birth of a child with fully symptomatic DGS. Both mothers had a mild form of VCFS and both had significant and prolonged low platelet counts. Thrombocytopenia is not a classical manifestation of either DGS or VDFS. Recently, Budarf et al. [1994] reported on a case of 22q11 deletion associated with Bernard-Soulier syndrome. This rare congenital bleeding disorder, characterized by thrombocytopenia and very large platelets, is associated with a defect in glycoprotein 1b (GP1b), the major platelet receptor for von Willebrand factor. As the Gp1bβ has been localized within the DG critical region, the authors postulated that the haploinsufficiency of 22q11 in this patient unmasked a mutation in the other allele. In our first patient, this condition can be clearly excluded because there were no giant platelets and because GP1b was normally expressed on the platelet membrane. In both patients, the clinical course suggests ITP. Two cases of DGS with ITP have been reported so far [Jyonouchi et al., 1991]. Of course, this occurrence could be coincidental. However, defective thymic function may predispose patients with DGS to autoimmune diseases. The two cases reported here suggest that patients with minimal clinical expression, such as parents of children with typical DGS, are also predisposed to ITP and that these ITP might be due to subtle dysfunction of T-cell regulation. Moreover, these two observations underline that ITP can be the first apparent pathologic event in the life of patients with the 22q11 microdeletion.

Careful examination of the clinical history of parents carrying the 22q11 microdeletion will certainly lead to a better definition of the long-term prognosis of deletion 22q11.

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